Health Based Guidance for Water
Health Risk Assessment Unit, Environmental Health Division
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# Toxicological Summary for: Perfluorohexane sulfonate

CAS: 108427-53-8 (anion)
355-46-4 (acid)
3871-99-6 (potassium salt)

Synonyms: PFHxS; perfluorohexanesulfonic acid; 1,1,2,2,3,3,4,4,5,5,6,6,6-tridecafluorohexane-1-sulfonate

**Short-term, Subchronic and Chronic* Non-Cancer Health Based Value (nHBV) = 0.047 µg/L****

*Due to the highly bioaccumulative nature of PFHxS within the human body, serum concentrations are the most appropriate dose metric and the standard equation to derive the HBV is not appropriate. Short-term exposures have the potential to stay in the body for an extended period of time. In addition, accumulated maternal PFHxS is transferred to offspring (i.e., placental and breastmilk transfer). A single HBV has therefore been recommended for short-term, subchronic, and chronic durations. The 2019 HBV was derived using a toxicokinetic (TK) model previously developed by MDH (Goeden 2019). Model details and results are presented below.

**Relative Source Contribution (RSC): Using the most recent published biomonitoring results (CDC 2018, 2019) and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, Section IV.E.1., an RSC of 0.5 (50%) was selected.

Intake Rate: In keeping with MDH's peer-reviewed and promulgated methodology, 95$^{th}$ percentile water intake rates (Table 3-1 and 3-3, USEPA 2011) or upper percentile breastmilk intake rates (Table 15-1, USEPA 2011) were used. Breastmilk concentrations were calculated by multiplying the maternal serum concentration by a PFHxS breastmilk transfer factor of 1.4%. For the breast-fed infant exposure scenario, a period of exclusive breastfeeding for one year was used as representative of a reasonable maximum exposure scenario. [Note: "exclusively breast-fed" intake rates refers to infants whose sole source of milk comes from human breastmilk, with no other milk substitutes (USEPA 2011, page 15-2).]

A simple equation is typically used to calculate HBVs at the part per billion level with results rounded to one significant digit. However, the toxicokinetic model used to derive the HBV for PFHxS showed that serum concentrations are impacted by changes in water concentrations at the part per trillion level. As a result, the 2019 HBV contains two digits.

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|---|---|
| Reference Dose/Concentration: | HED/Total UF = 0.00292/300 = 0.0000097 mg/kg-d (or 9.7 ng/kg-d) (adult Sprague Dawley rats). [The corresponding serum concentration is 32.4/300 = 0.108 µg/mL. Note: this serum concentration is inappropriate to use for individual or clinical assessment.***] |
| Source of toxicity value: | Determined by MDH in 2019 |
| Point of Departure (POD): | 32.4 µg/mL (or mg/L) serum concentration (male rats - NTP 2018, MDH modeled $BMDL_{20\%}$) |
| Dose Adjustment Factor (DAF): | Toxicokinetic Adjustment based on Chemical-Specific Clearance Rate = Volume of Distribution (L/kg) x (Ln2/Half- |

| | |
|---|---|
| | life, days) = 0.25 L/kg x (0.693/1935 days) = 0.000090 L/kg-day. (Half-life from Li et al 2018) |
| Human Equivalent Dose (HED): | POD x DAF = 32.4 mg/L x 0.000090 L/kg-d = 0.00292 mg/kg-d |
| Total uncertainty factor (UF): | 300 |
| Uncertainty factor allocation: | 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 10 for database uncertainty to address concerns regarding early life sensitivity to decreased thyroxine (T4) levels as well as lack of 2 generation or immunotoxicity studies. |
| Critical effect(s): | decreased free T4 |
| Co-critical effect(s): | decreased free and total T4, triiodothyronine (T3), and changes in cholesterol levels and increased hepatic focal necrosis |
| Additivity endpoint(s): | Hepatic (Liver) System and Thyroid (E) |

***The serum concentration is useful for informing public health policy and interpreting population-based exposure potential. This value is based on population-based parameters and should not be used for clinical assessment or for interpreting serum levels in individuals.

Toxicokinetic Model Description (Goeden 2019):

PFHxS is well absorbed and is not metabolized. Serum concentrations can be calculated from the dose and clearance rate using the following equation.

$$\textbf{Serum Concentration}\left(\frac{mg}{L}\right) = \frac{\textbf{Dose}\left(\frac{mg}{kg \cdot day}\right)}{\textbf{Clearance Rate}\left(\frac{L}{kg \cdot day}\right)}$$

*Where:*

*Dose (mg/kg-day) = Water or Breastmilk Intake (L/kg-day) x Water or Breastmilk Concentration (mg/L)*
*and*
*Clearance (L/kg-day) = Volume of distribution (L/kg) x (Ln 2/human half-life, days)*

Two exposure scenarios were evaluated: 1) an infant fed formula reconstituted with contaminated water starting at birth and continuing ingestion of contaminated water through life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking contaminated water. In both scenarios the simulated individuals began life with a pre-existing body burden through placental transfer of PFHxS (maternal serum concentration x 70%) based on median cord to maternal serum concentration ratios reported in the literature. The serum concentration of the mother at delivery was assumed to be at steady-state and was calculated by using the equation above with a time-weighted 95$^{th}$ percentile intake from birth to 30 years of age (0.047 L/kg-d). During lactation a 95$^{th}$ percentile water intake rate of 55 mL/kg-d and a body weight of 65.2 kg ((USEPA 2011), Table 3-3) was used to calculate daily maternal serum concentrations.

Consistent with MDH methodology, 95th percentile water intake and upper percentile breastmilk intake rates were used to simulate a reasonable maximum exposed individual. A PFHxS breastmilk transfer factor of 1.4%, based on average breastmilk to maternal serum concentration ratios reported in the literature, was used to calculate breastmilk concentration. According to the 2016 Breastfeeding Report Card (CDC, 2016), nearly 66 percent of mothers in Minnesota report breastfeeding at six months, dropping to 41% at twelve months. MDH chose to use the breastmilk intake rates for exclusively breastfed infants, as reported in USEPA 2011, for one year for the breast-fed infant scenario.

Daily post-elimination serum concentration was calculated as:

$$Serum\ Conc.\left(\frac{mg}{L}\right) = \left[Prev.\ day\ Serum\ Conc.\left(\frac{mg}{L}\right) + \frac{Today's\ Intake(mg)}{V_d\left(\frac{L}{kg}\right) \times BW(kg)}\right] \times e^{-k}$$

To maintain mass balance, daily maternal serum concentrations and loss-of-chemical via transfer to the infant as well as excretion represented by the clearance rate, were calculated.

Summary of Reasonable Maximum Exposure (RME) Scenario Model Parameters

| Model Parameter | Value Used |
|---|---|
| Volume of distribution (Vd) | 0.25 L/kg (average of male (0.287) and female (0.213) nonhuman primate Vd, Sundstrom, 2012) |
| Vd Age Adjustment Factor | 2.1 age 1-30 days decreasing to 1.2 age 5-10 years and 1.0 after age 10 years (Friis-Hansen 1961) |
| Half-life | 1935 days (mean value for all ages, Li et al 2018)<br>(5th to 95th percentile range: 1095 – 3358 days) |
| Elimination rate constant (k) | Calculated from Ln 2/half-life |
| Placental transfer factor<br>*(% of maternal serum level)* | 70% (mean of median paired maternal:cord blood ratios reported in the literature. Range of mean values 43 – 95%.)<br>(Mean 95th percentile value 110%, range 69 – 168%.) |
| Breastmilk transfer factor<br>*(% of maternal serum level)* | 1.4% (mean of mean paired maternal serum:breastmilk ratios reported in the literature. Range of mean values 0.8 – 2%.)<br>(No 95th percentile values reported in literature.) |
| Water Intake Rate (L/kg-d) | 95th percentile consumers only (default values, MDH 2008) (Table 3-1 & 3-3, USEPA 2011) |
| Breastmilk Intake Rate (L-kg-d) | Upper percentile exclusively breast-fed infants (Table 15-1, USEPA 2011) |
| Body weight (kg) | Calculated from water intake and breastmilk intake rate tables |

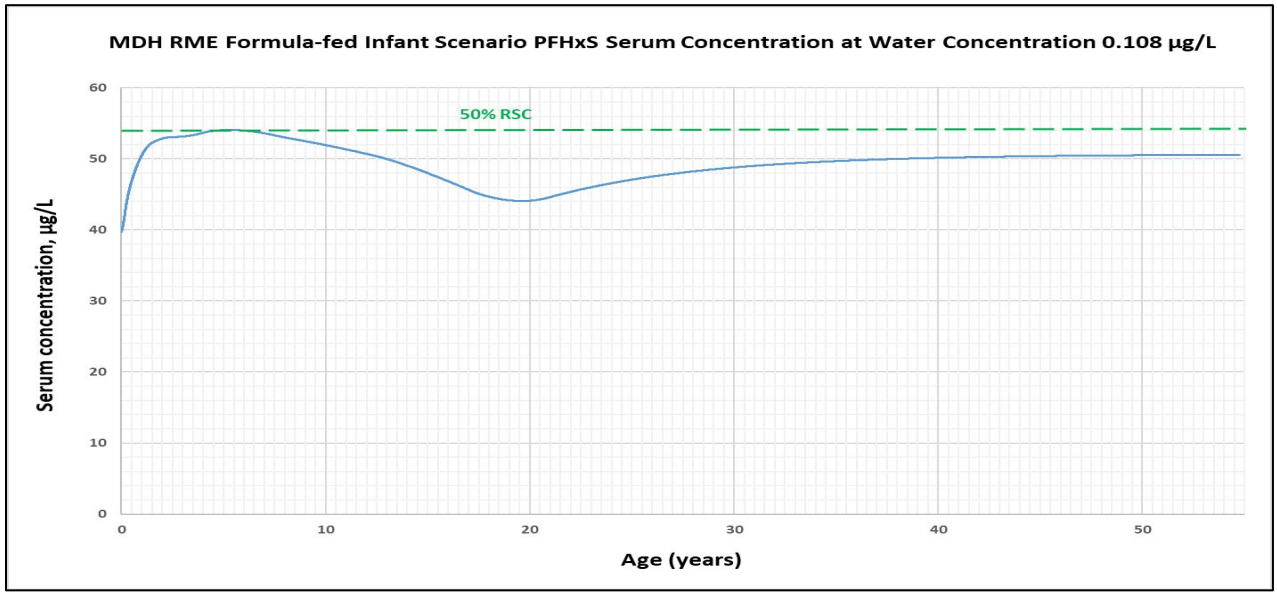
A relative source contribution factor (RSC) is incorporated into the derivation of a health-based water guidance value to account for non-water exposures. MDH utilizes the Exposure Decision Tree process presented in USEPA 2000 to derive appropriate RSCs. Determination of an appropriate RSC must recognize the long elimination half-life of PFHxS, such that a person's serum concentration at any given

age is not only the result of his or her current or recent exposures within the duration of concern, but also from exposure from years past.

Human biomonitoring data provide a quantitative description of the ongoing widespread exposure, but the serum data are not informative as to the specific pathways and exposure routes. The most recently reported 95$^{th}$ percentile serum concentrations from CDC (2019) range from 1.62 µg/L serum for young children to nearly 5 µg/L serum for older children and adults. This suggests that 'background' exposures, when compared to the 'reference' serum concentration (108 µg/L serum) would not represent significant sources of exposure. Using the most recent published biomonitoring results and USEPA's Exposure Decision Tree (USEPA 2000) as outlined in MDH 2008, an RSC of 0.5 (50%) was selected.

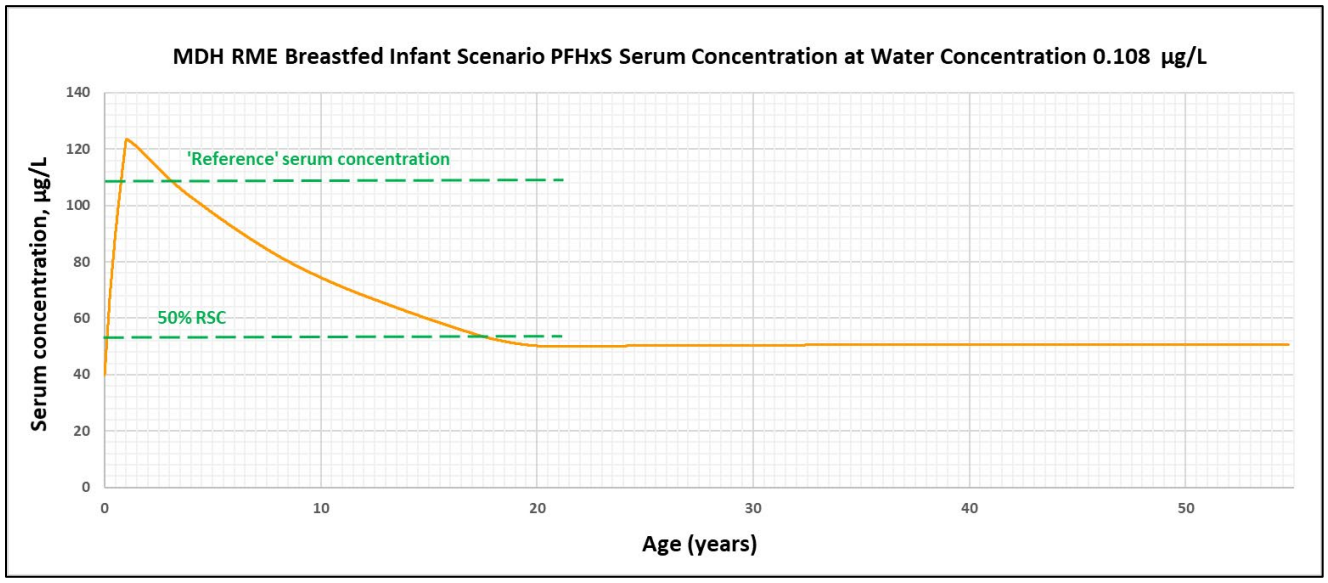
As mentioned above, two exposure scenarios were examined: 1) an infant fed formula reconstituted with PFHxS-contaminated water starting at birth and continuing ingestion of contaminated water throughout life; and 2) an infant exclusively breast-fed for 12 months, followed by drinking PFHxS-contaminated water throughout life. For the first scenario, the formula-fed infant, the water concentration that maintains a serum concentration attributable to drinking water at or below an RSC of 50% is 0.108 µg/L (Figure 1).

Figure 1. Exclusively formula-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and an RSC of 50%.



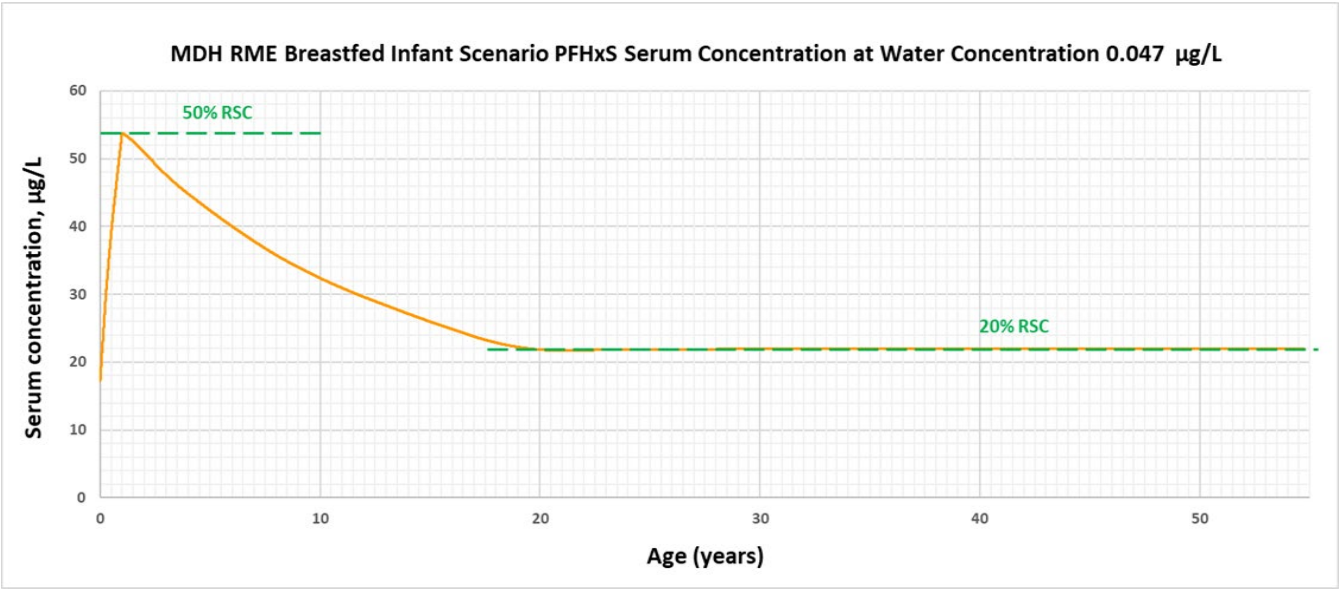

Applying this water concentration (0.108 µg/L) in the context of the breast-fed infant resulted in serum PFHxS concentrations exceeding the 'reference' serum concentration for nearly 2 years, and the 50% RSC threshold for nearly 17 years. See Figure 2.

Figure 2. Breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME and a water concentration of 0.108 µg/L.




In order to maintain serum concentrations at or below an RSC of 50% for breast-fed infants, the water concentration should not exceed 0.047 µg/L; see Figure 3. This water concentration also produces steady state serum concentrations at approximately 20% of the 'reference' serum concentration.

Figure 3. Exclusively breast-fed infant scenario serum concentrations over a lifetime, based on MDH's RME, and a water concentration of 0.047 µg/L.




**To ensure protection of all segments of the population, the final health-based value for PFHxS is set at 0.047 µg/L.**

**Cancer Health Based Value (cHBV) = Not Applicable**

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|---|---|
| Cancer classification: | Not Classified |
| Slope factor (SF): | Not Applicable |
| Source of cancer slope factor (SF): | Not Applicable |
| Tumor site(s): | Not Applicable |

**Volatile:** Yes (moderate)

**Summary of Guidance Value History:**

MDH first reviewed PFHxS in 2009 and determined that there was insufficient data to derive a value. In 2013, MDH's Site Assessment and Consultation Unit began using the guidance value for PFOS as a surrogate to assess potential risks from exposure to PFHxS, in the absence of adequate chemical specific data. In 2018 additional toxicokinetic and toxicity information became available. In 2019, MDH derived a noncancer HBV (applicable to short-term, subchronic, and chronic durations) of 0.047 µg/L.

**Summary of toxicity testing for health effects identified in the Health Standards Statute (144.0751):**

Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. MDH has considered the following information in developing health protective guidance.

| | Endocrine | Immunotoxicity | Development | Reproductive | Neurotoxicity |
|---|---|---|---|---|---|
| Tested for specific effect? | Yes | No | Yes | Yes | Yes |
| Effects observed? | Yes[1] | -[2] | No[3] | Yes[4] | No[5] |

**Comments on extent of testing or effects:**

[1] Several human epidemiological studies have evaluated the possible association between serum PFHxS and alterations in thyroid hormone levels. Two studies found an association in women between serum PFHxS and thyroid hormone levels, however, other studies did not find this association. Two general population epidemiology studies have evaluated associations between PFHxS and reproductive hormones, finding no association.

Based on studies in laboratory animals, alterations in serum thyroid hormone levels, in particular thyroxine (T4), appear to be a sensitive effect. The POD is based on decreased serum T4 levels in adult male rats however, decreased serum T4 levels have also been reported in pregnant and lactating rats and pups. Unfortunately, serum PFHxS levels were not measured in pregnant or lactating rats or pups at the NOAEL and LOAEL dose levels, however, study results suggest that pups may be more sensitive than adult nonpregnant animals. A database uncertainty factor (DB UF) has been incorporated into the RfD derivation, in part, due to concerns that early life stages may be more sensitive.

Androgenic effects have also been evaluated in laboratory animals to a limited extent. No changes in adult male reproductive organ weights or sperm parameters were observed at serum levels up to ~600-fold higher than the 'reference' serum concentration. Androgenic activity was also evaluated in pups exposed in utero and through lactation. No significant effects were observed on anogenital distance, nipple retention, or reproductive organ weights at serum levels ~1300-fold higher than the 'reference' serum concentration.

[2] Several epidemiology studies have examined the potential association between PFHxS and suppression of the immune system. Inverse or no associations were observed in these studies. In general, available studies have not found an association between PFHxS and infectious disease resistance or with hypersensitivity outcomes.

Immunotoxicity has not been studied in laboratory animals. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[3] General population epidemiology studies have evaluated potential associations between maternal PFHxS and a variety of birth outcomes. A couple of studies have reported associations with birth weight or neurobehavioral outcome but others found no association.

Reproductive/developmental screening studies in rats and mice have not found treatment related changes in development outcome, including neurobehavioral effects, at serum levels $\geq$ ~900-fold higher than the 'reference' serum concentration. Neurobehavioral outcomes were also evaluated in a study using a single oral exposure to neonatal mice on postnatal day 10. No serum levels were measured and therefore, the results could not be quantitatively incorporated into MDH's assessment. No 2-generation study has been conducted. A DB UF has been incorporated into the RfD derivation, in part, to address this data gap.

[4] In general, epidemiology studies evaluating potential associations between PFHxS and reproductive measures have not found any associations. A small number of studies have reported associations with earlier menopause or time to pregnancy. However, since menstruation, childbirth, and lactation are potential elimination routes for women this could confound the associations.

Laboratory studies in rats did not find changes in reproductive parameters at serum levels $\geq$ ~1600-fold higher than the 'reference' serum concentration. A decrease in the number of pups per litter has been reported in mice, however the dose-response curve was flat and there was no difference in the number of pups born to the implant ratio. The 'reference' serum concentration is ~500-fold lower than the serum concentrations at which this effect occurs in mice, therefore the RfD is protective for this potential effect.

[5] Two epidemiology studies have evaluated association between PFHxS serum levels and self-reported memory loss or periods of confusion. One study reported a decrease in risk at the fifth quintile whereas the second study found no association.

Laboratory animal studies have evaluated neurotoxicity using the functional observation battery (FOB) and motor activity assessment. No effects were observed on adult rats and mice at serum concentrations ≥~600-fold higher than the 'reference' serum concentration. Potential neurological effects have also been evaluated in rat pups using these same evaluation tools. No effects were observed at serum concentrations up to ~800-fold higher than the 'reference' serum concentration. A neurotoxicity evaluation following a single oral dose to neonatal animals has also been conducted. See footnote #3 above.

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